M E M O R A N D U M

TO: Alan C. Lloyd, Ph.D.
Agency Secretary
California Environmental Protection Agency

FROM: Joan E. Denton, Ph.D.
Director

DATE: April 1, 2005

SUBJECT: RESPONSES TO RECENT COMMENTS ON THE PERCHLORATE PHG

The Office of Environmental Health Hazard Assessment (OEHHA) released the final Public Health Goal (PHG) for perchlorate in March 2004 (Health and Safety code section 116365(e)(1)). At the time, OEHHA knew the National Academy of Sciences (NAS) was conducting a scientific review of U.S. EPA's 2002 Draft Toxicological and Risk Characterization for Perchlorate and promised to evaluate the findings and recommendations of the NAS when it became available, and revise the PHG as necessary.

On January 11, 2005, NAS released its review in a report titled "Health Implications of Perchlorate Ingestion." Since then, OEHHA has received several comments offering suggestions or requesting changes in the perchlorate PHG. In the technical summary attached to this memorandum, OEHHA provides responses to these recent comments and our conclusion as to the need for a formal update of the perchlorate PHG document.

After carefully reviewing the NAS report, OEHHA concludes that the approach we used in developing the perchlorate PHG is valid. The NAS report did not provide "new scientific evidence" indicating that perchlorate "presents a materially different risk to public health than was previously determined."

OEHHA acknowledges the disparate comments from the interested parties, and that other ways of looking at the available data can lead to either higher or lower estimated health-protective levels. However, the arguments that have been offered are essentially the same as considered earlier by OEHHA, and also by the NAS committee.

Therefore, there does not appear to be any new scientific evidence for OEHHA to revise the perchlorate risk assessment, nor alter the estimated health-protective drinking water concentration of 6 ppb (6 µg/L) that is stated in the final PHG document.

If you have any questions or would like to discuss this issue, please call me at 322-6325.

Attachments

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CCA 05-0009

Response to Comments on the Perchlorate Public Health Goal (PHG) Since the Release of the National Academy of Sciences (NAS) Committee Report on Perchlorate.

The NAS report made four key findings that strongly support the approach that OEHHA used in developing the PHG. These findings are:

1. The health effects of perchlorate should be assessed using data from human studies, rather than animal studies. The NAS specifically recommended the use of the 2002 study by Greer, et al., in which healthy volunteers were administered perchlorate. OEHHA used data from the same study in its perchlorate risk assessment.

2. The perchlorate health effect of primary concern is the reduction of the uptake of iodide by the thyroid gland. While not harmful by itself, inadequate iodide uptake may lead to the harmful disruption of proper thyroid function. The NAS report said that the reduction of iodide uptake "is the key event that precedes all thyroid-mediated effects of perchlorate exposure," and that focusing on the reduction of iodide uptake "is the most health protective and scientifically valid approach." OEHHA's assessment similarly focused on the reduction of iodide uptake as the critical health effect.

3. The NAS report identified fetuses of pregnant women as the most sensitive subpopulation. OEHHA similarly concluded that pregnant women and fetuses are the most sensitive subpopulation.

4. The NAS recommended an uncertainty factor of 10 to ensure adequate protection of pregnant women and fetuses. OEHHA used the same uncertainty factor in calculating the PHG.

OEHHA did not find any statements in the NAS report that conflicted with OEHHA's approach in developing the PHG. However, there are two important areas of difference between the NAS report and OEHHA's assessment. These differences are:

1. The NAS report did not calculate a safe level of perchlorate in drinking water, as this was outside the request made to the NAS. Additional calculations not addressed in the NAS report are necessary to develop a PHG, such as accounting for an individual's exposure to perchlorate from food and other sources besides drinking water.

2. The NAS report calculated a reference dose after first identifying a No Observable Effect Level or NOEL (a generic number identifying a level or perchlorate exposure from any source that would not cause a health effect). OEHHA used a statistical method called the "benchmark dose" to identify a level of perchlorate exposure that would not cause a health effect. A PHG can be calculated from either a NOEL or benchmark dose, and both numbers in this case were obtained using data from the Greer study. The benchmark dose approach is preferred when the number of subjects in a study is relatively small, as

in the Greer study, because it involves a statistical analysis and calculation of a 95-percent confidence level using all data points from the study. The NOEL, in contrast, is calculated using only the relatively few data points that appear to identify a no observable effect level. The NAS report said the benchmark dose "can be an improvement" over other approaches, but used the NOEL approach rather than choose between several methods for calculating a benchmark dose.

A summary of the major recent comments and our responses to them follows:

Commenter 1. Several environmental groups[1] petitioned OEHHA to revise the PHG to no higher than 1 ppb; they also petitioned DHS to immediately issue an emergency MCL for perchlorate at a level no higher than the PHG.

While the petition supported OEHHA's decision to use a benchmark dose approach in identifying a threshold for the reduction of thyroidal iodide uptake, it faulted OEHHA for not using body weight and water/milk consumption rate of an infant in deriving the PHG. The petition asked OEHHA to revise the PHG; it showed that using exposure parameters specific to an infant, a 10-fold uncertainty factor, and a relative source contribution of 0.2, the PHG could be as low as 0.4 ppb. Other combinations of health-protective estimates and exposure parameters could result in a PHG from 0.4 to 2.5 ppb.

Response 1: While an infant is one of the populations of concern, infants are not considered as sensitive as the pregnant woman and her fetus, based on both biological and effective dose-rate calculations. Although there is no recognized iodine-deficient fraction of the general population, pregnant women are considered to be more likely to be iodide deficient because they have a greater need for iodide and at the same time have a higher urinary iodide excretion rate.

As indicated in the PHG document, perchlorate is not retained by the body to any significant extent. The increased relative fluid intake rate of infants, balanced by the increased urinary excretion rate, does not appear to lead to a higher blood concentration of perchlorate in infants, compared to adults. In their January 22, 2003 memorandum, United States Environmental Protection Agency (U.S. EPA) stated "The uptake and elimination kinetics of perchlorate for children are such that traditional adjustment of exposure based on body weight scaling results in exposure estimates equivalent to those for adults." No information was provided in the comments that indicate this conclusion was incorrect.

For all these reasons, OEHHA believes that the existing PHG is adequately protective for all sensitive subpopulations, including infants, and does not intend to revise the PHG support document at this time.

Commenter 2. The Association of California Water Agencies (ACWA) requested OEHHA to make a decision regarding the PHG as quickly as possible as this will permit DHS to develop a perchlorate MCL in a timely manner. ACWA also expressed its strong opposition to the suggestion that DHS adopt an emergency MCL for perchlorate while the PHG is being revised because this would cause delays and uncertainties for local water agencies that are seeking to recover cleanup costs from responsible parties.

[1] Center for Community Action and Environmental Justice, Citizens for Chuckwalla Valley, Clean Water Action, Environment California, Environmental Working Group, Natural Resources Defense Council, Sierra Club-California, INSIST, San Martin Community Representative.

Response 2: OEHHA understands ACWA's concerns and considers that no changes are needed in the PHG level. We understand that the state will be moving forward with the development of a MCL.

Commenter 3: Member companies of the Perchlorate Study Group (PSG), with the exception of Lockheed-Martin Corporation, petitioned OEHHA to raise the perchlorate PHG. The preferred PHG level was provided as 236 ppb, but additional potential values of 167 ppb, or as low as 16 ppb, were discussed with different scenarios.

The commenters suggested that since the NAS has identified 0.007 mg/kg-day as the No Observed Effect Level (NOEL), the NAS has effectively established a floor for the "safe dose response threshold" at the NOEL. If one uses the NOEL as the point of departure, the default body weight of 70 kg, and the default water consumption rate of 2 L/day, this would yield a drinking water level of 245 ppb (without relative source contribution). Based on the urinary perchlorate data from the Centers for Disease Control, it is estimated that exposures to perchlorate from food sources is approximately equivalent to a water level of 9 ppb. Subtracting this from 245 ppb, a value of 236 ppb can be calculated.

Alternatively, the PSG suggested that one could use the NOEL as the point of departure and apply the body weight and water consumption rate of a pregnant woman for the calculation of a water level. This would give a water level of 176 ppb. After adjusting for perchlorate in food, a level of 167 ppb results. However, if one applies an uncertainty factor of 10 to the NOEL as recommended by the NAS and uses the default body weight and water consumption rate, one would arrive at a water level of 25 ppb. Adjusting for perchlorate in food would yield a value of 16 ppb. The commenter stated that further adjustment for variations in body weight and water consumption rate in the population is not necessary in this case as the variations are already accommodated in the 10-fold uncertainty factor.

The PSG emphasized that the three calculations described above are extremely conservative as they are all based on the NOEL, not the NOAEL. The commenter stated that there is a statutory obligation that the PHG must be set at the NOAEL. The commenter also claimed that the choice of a NOEL as the point of departure is unprecedented, and that none of the many drinking water standards developed by U.S. EPA and OEHHA have been based on a NOEL.

Finally, the PSG also suggested that there are at least two PHG chemicals, nitrate and thiocyanate, that also reduce iodide uptake by the thyroid. If OEHHA were to use the approach used in the perchlorate PHG on these two chemicals, the revised nitrate and thiocyanate PHGs would be dramatically reduced – equivalent to 190 µg/L and 670 µg/L, respectively. These levels are much lower than their current PHGs and could have significant consequences for the food supply if such levels were even attainable.

Response 3: The NAS committee identified 0.4 mg/kg-day as the NOAEL for <u>healthy adults</u>. However, the committee recognized that this level may not be low enough to protect the most

sensitive individuals, such as pregnant women and their fetuses, especially if they are iodide deficient. As OEHHA had done earlier, the committee chose to focus on inhibition of iodine uptake, and concluded that if this first step in the chain of perchlorate actions does not occur, all other adverse health effects of perchlorate exposure will be prevented.

In the NAS report, the committee stated that the choice of a NOEL as the point of departure is unusual, but that given the current scientific knowledge and the need to protect the sensitive subgroups, it is prudent to choose reduction of thyroidal iodide uptake as the endpoint. OEHHA also believes that this endpoint is the prudent choice. By choosing a perchlorate level that does not lead to a reduction in iodide uptake, OEHHA fulfills the requirements described in the California Safe Drinking Water Act, Health and Safety Code §§ 116365:

- OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness, and
- OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.

OEHHA disagrees with the comment that the use of a NOEL as the point of departure in human health risk assessment is unprecedented. There are at least 23 chemicals in the U.S. EPA Integrated Risk Information System (IRIS) whose evaluations are based on no observed effect levels (see Appendix I). PHGs for several chemicals are also based on effects other than the standard "adverse" effects of classical toxicology (aluminum, barium, fluoride, lead, thallium, xylene, and others). However, making a complete list of such chemicals is complicated by the fact that in the drinking water program OEHHA has declined as a matter of policy to distinguish between NOELs and NOAELs in the risk assessments, to make the point that many effects other than frank toxicity are worthy of attention. Biochemical markers such as altered serum enzyme levels, or other parameters such as behavioral endpoints, have been used as extensively by OEHHA as by U.S. EPA, over the years.

OEHHA disagrees with the comment that given the health protective nature of the critical end-point chosen, it is not necessary to apply an uncertainty factor of 10. All participants in the Greer et al. (2002) study[2] were healthy adults. There is uncertainty in extrapolating the study result to more sensitive fetuses, pregnant women, infants, and individuals with impaired thyroid functions. There is also a concern for the potential synergistic effect of other goitrogens in the environment and food. For these reasons, OEHHA believes it is necessary to retain the 10-fold uncertainty factor in the PHG.

In the perchlorate PHG calculation, OEHHA used body weight and water consumption rate information specific to pregnant women, the most sensitive subgroup. Default parameters are used only when there is no specific sensitive subgroup identified. The relative source

[2] Greer et al. (2002). Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans. Environmental Health Perspectives 110 (9):927-937.

contribution used to allow for other perchlorate sources was based on the data available at the time. Subsequent studies have confirmed that perchlorate is widespread in milk and lettuce in the U.S., but have not yet adequately addressed all the potential food sources.

OEHHA is aware that nitrate and thiocyanate can also reduce uptake of iodide into the thyroid, but there is no PHG for thiocyanate. Based on our preliminary review of the scientific literature, these two chemicals appear to be much less potent than perchlorate as iodide uptake inhibitors.

Commenter 4: A consortium of business groups[3] requested OEHHA to revise the perchlorate risk assessment and set a PHG utilizing the approach and reference dose used by the NAS. The letter stated that because the reference dose is based on a non-adverse health effect plus a 10-fold safety factor to protect sensitive subgroups, a value based on this approach should be adequately health protective. It is said that "under no circumstances can the statute [HSC 116365(c)(1)(D)] be interpreted to support a PHG lower than 25 ppb. However, it then goes on to say "the only additional adjustment, in light of regulatory precedent, would be for exposures to perchlorate from food and other non-water sources."

Response 4: It is important to note that the NAS did not calculate a drinking water level for perchlorate. NAS said in their press conference that in order to calculate a drinking water level from their reference dose one needs to consider: (a) relative source contribution and (b) the body weight and drinking water consumption amounts of the target population. The NAS report does not provide any guidance regarding these estimations. At the NAS reference dose of 0.0007 mg/kg-day with the default assumptions of 70 kg for body weight and 2 L/day for drinking water consumption, the drinking water level would be 25 ppb; use of a relative source contribution of 0.2 (the U.S. EPA default value) would yield a health-protective value of 5 ppb.

The major difference between the two risk assessments is that the NAS chose to use the NOEL (0.007 mg/kg-day) of the thyroidal iodide uptake data reported by Greer et al. (2002) as the point of departure for the calculation of the RfD, while OEHHA applied a benchmark dose model to analyze the same data set and estimated a threshold of 0.0037 mg/kg-day. OEHHA proposed a NOEL approach in the first public draft of the perchlorate PHG. OEHHA responded to public and peer review comments by changing the NOEL approach to the benchmark dose approach. In general, the benchmark dose model is better because it takes into account the range of doses used, sample size, and variability of response. Both industry and government risk assessors are recommending benchmark approaches as scientifically more reliable. However, using the

[3] Alliance of Automobile Manufacturers, American Forest and Paper Association, California Building Industry Association, California Business Properties Association, California Chamber of Commerce, California Council for Environmental and Economic Balance, California Grocers Association, California Healthcare Institute, California Independent Oil Marketers Association, California Independent Petroleum Association, California Manufacturers and Technology Association, California Mining Association, California Natural Gas Producers Association, California Paint Council, California Retailers Association, California Space Authority, Consumer Specialty Products Association, Grocery Manufacturers of America, Industrial Environmental Association, Western States Petroleum Association

method recommended by the NAS committee and the default U.S. EPA exposure parameters yields a value very similar to the existing PHG.

For these reasons, OEHHA believes the current PHG is consistent with the findings and recommendations of the NAS, and has no plans for any immediate revisions of the PHG support document.

Commenter 5: An agricultural coalition[4] urged OEHHA to use the advice provided by the NAS perchlorate review committee. The letter claimed that the reference dose set by the NAS committee is many times higher than OEHHA's current PHG, and urged OEHHA to harmonize the PHG with the recommendations of the NAS. It is said that the use of a NOEL was an "unprecedented 'ultra-conservative' standard" for derivation of the RfD. Since the NAS reference dose is based on a non-adverse effect with an uncertainty factor of 10 to account for human variability, the commenters affirm that the reference dose is protective of all individuals, including sensitive subpopulations, for both chronic and acute exposure to perchlorate.

Response 5: OEHHA agrees with the commenters that the NAS committee report is a valuable and important contribution to the scientific discussion about perchlorate toxicity. The committee has chosen to use the approach utilized earlier by OEHHA to determine a health-protective dose in drinking water, based on inhibition of iodine uptake in the study of Greer et al. The relatively small difference in safe dose of perchlorate derived by the committee, compared to OEHHA, is because NAS chose not to use the benchmark modeling method, which was recommended by our earlier peer reviewers.

The NAS reference dose (0.0007 mg/kg-day) is about twice the health-protective dose that can be derived from our risk assessment of 0.00037 mg/kg-day (0.0037 mg/kg-day divided by the uncertainty factor of 10). Differences in estimation of health-protective values by only a factor of two, as in this case, are normally considered acceptable (confirmatory).

The use of a NOEL by NAS is by no means unprecedented in risk assessment, as can be seen by examining the RfDs listed in U.S. EPA's IRIS database. At least 23 values were derived using NOELs over the last two decades, as summarized in Appendix I below. Derivation of an RfD from these values involved application of uncertainty factors up to 3,000, depending on the source and quality of the supporting data. In no case was an uncertainty factor less than 10 applied. The NAS and OEHHA approach to risk assessment of perchlorate is therefore seen to be consistent with precedents established over many years by the U.S. EPA.

[4] Western Growers, California Grain and Feed Association, California Seed Association, Western Plant Health Association, Grower-Shipper Association of Central California, Imperial Valley Vegetable Growers Association, Coalition of Labor, Agriculture and Business for the Imperial County, California Minor Crops Council, California League of Food Processors, Ventura County Agricultural Association, Produce Marketing Association, Monterey County Farm Bureau, California Citrus Mutual, Alliance of Western Milk Producers, California Cotton Growers Association, Nisei Farmers League, International Fresh Cut Produce Association, California Farm Bureau Federation.

OEHHA agrees that basing the RfD, and also the PHG level, on avoidance of iodide uptake is conservative in the health-protective sense. We believe that a health-protective approach is required by the California Safe Drinking Water Act. Applying standard U.S. EPA exposure parameters to the RfD would yield a value of 5 ppb.

Commenter 6: Dr. Sanchez sent a letter to OEHHA that provides results of his recent work regarding perchlorate concentrations in lettuce, for our consideration in future revisions of the PHG.

Response 6: OEHHA thanks Dr. Sanchez for his interest in our drinking water program and his willingness to share his data with OEHHA. We appreciate his efforts in providing better data on food concentrations of perchlorate, so that the sources of perchlorate can be better defined.

Appendix I

In the following list, examples of chemical risk assessments performed by U.S. EPA are provided in which use of NOELs has been explicitly identified in the critical study, as summarized in the IRIS database. Although many different effects are noted, none of these are considered by the U.S. EPA to be an "adverse" effect, and in some cases, no effect at all was observed in the critical study.

NOELs Used by U.S. EPA as listed in the IRIS database*

	Chemical	Endpoint	Last Revised	UF
1	Acephate	Inhibition of brain AChE	1990	30
2	Alar	No adverse effects	1987	100
3	Amdro	Increased organ weights	1987	1000
4	Amitraz	Increased blood sugar, hypothermia	1987	100
5	Anthracene	No observed effects	1993	3000
6	Bromoxynil	No adverse effects	1988	300
7	Bromoxynil octanoate	No effects	1988	300
8	Butylphthalyl butylglycolate	No adverse effects	1988	1000
9	Chlorpyrifos	Decreased plasma ChE	1988	10
10	Diflubenzuron	Met- and sulf-hemoglobinemia	1990	100
11	Diisopropyl methylphosphanate	No effects	1993	1000
12	Dimethoate	Brain AChE inhibition	1990	300
13	Diuron	Abnormal pigments in blood	1988	300
14	Ethion	Plasma ChE inhibition	1989	100
15	Express	Elevated serum bilirubin & AST, increased urine volume	1990	100
16	Fenamiphos	ChE inhibition	1990	100
17	Malathion	RBC ChE inhibition	1992	10
18	Naled	Brain AChE inhibition	1995	100
19	NuStar	Liver cell enlargement	1991	300
20	Pirimiphos-methyl	Plasma ChE inhibition	1992	25
21	Pronamide	No effects	1994	100
22	Quinalphos	No adverse effects	1992	100
23	Tetraethyldithiopyrophosphate	Decreased plasma and RBC ChE	1995	1000

*More than a dozen additional chemicals are based on a study in which no adverse effects were reported, but the IRIS file nevertheless reports them as being based on a "NOAEL."